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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/700,599	11/04/2003	Bernd Bohrmann	21459	6499

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PATENT LAW DEPARTMENT
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EXAMINER	
MARTIN, PAUL C	
ART UNIT	PAPER NUMBER
1655	

DATE MAILED: 04/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/700,599	BOHRMANN ET AL.	
	Examiner	Art Unit	
	Paul C. Martin	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13 and 15-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13 and 15-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-11, 13 and 15-22 are pending in this application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

All objections and rejections not repeated in the instant Action have been withdrawn due to Applicant's response to the previous Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 18 recites the "...with the help of..." It is unclear whether or not this constitutes another method step. If so, correction is required. If the Applicant means by comparing peaks separated from the base-line peak pattern as a means of determining the amount of beta amyloid, then that constitutes a separate method step and should be more clearly delineated.

The following are New Rejections not necessitated by Applicant's amendment:

Claim Objections

Claim 6 is objected to because of the following informalities: The word "peptide is misspelled. Appropriate correction is required.

Claims 4 and 19 are objected to because of the following informalities: The word "aggregated" appears to be misspelled. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 2, 9, 11, 15, 16 and 17 rejected under 35 U.S.C. 103(a) as being unpatentable over Clarke *et al.* (2001) in view of Riek *et al.* (2001).

Clarke teaches a method for the quantification of beta amyloid in guinea pig brain cells by adding a defined amount of synthetically produced beta amyloid peptide to a cell lysate containing naturally produced oxidized beta-amyloid (Pg. 34, Column 2, Lines 6-21), preparing the isolated beta amyloid for analysis by mass spectroscopy (Pg. 35, Column 1, Lines 8-19), analyzing the prepared beta amyloid by mass spectroscopy (Pg. 35, Column 2, Lines 9-11), and determining the amount of beta amyloid present in the guinea pig brain cell lysate (Pg. 34, Column 2, Lines 9-13 and Pg. 36, Column 1, Lines 15-24 and Column 2, Lines 1-8 and Fig. 3).

Clarke *et al.* does not teach the preparation for analysis by mass spectroscopy by enzymatic digestion by a protease.

Clarke *et al.* does not teach the method of using MALDI-TOF mass spectroscopy.

Reik *et al.* teaches the use of recombinantly produced and labeled β-amyloid, wherein the β-amyloid is labeled with N^{15} (Pg. 5930, Column 2, Lines 30-31 and Pg. 5931, Column 1, Lines 4-8), and the use of enzymatic digestion with the protease Lys-C prior to analysis by mass spectroscopy (Pg. 5931, Column 1, Lines 19-21).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the method for quantifying the levels of β-amyloid taught by Clarke toward the detection of β-amyloid as taught by Reik because the ordinary artisan would have recognized that the method of Clarke could be adapted to the detection and quantitation of isotopically labeled β-amyloid. Reik and Clarke both teach the use of recombinant and synthetic β-amyloid respectively expressing methionine-oxidation and N^{15} labels for analysis by mass spectroscopy. The step of protease digestion would have been obvious to one of ordinary skill as a means of obtaining a mass fingerprint to be compared with a known standard similarly digested. Furthermore, since the methods already teach the use of mass spectroscopy, the use of alternative forms of mass spectroscopy such as MALDI-TOF would have been obvious. The ordinary artisan would have been motivated to combine the two methods in order to quantitatively measure the amounts of β-amyloid in a sample by comparing to recombinantly-produced, non-radioactive isotope labeled standard β-amlyoid.

The ordinary artisan would have had a reasonable expectation of success based upon the similarity of the two methods in using recombinantly-produced human proteins with non-radioactive isotope labels.

Claims 1, 2, 4, 7, 8, 9, 11, 13, 18, 19, 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Clarke *et al.* (2001) in view of Kametani *et al.* (1999) and Riek *et al.* (2001).

The teachings of Clarke and Riek were discussed above.

Clarke *et al.* does not teach the use of the method with aggregated, soluble β-amyloid peptides obtained from the source of a tissue sample are obtained through laser dissection excision, wherein the β-amyloid peptides are either amino or carboxy terminal microheterogenous.

Kametani *et al.* teaches a method for the semiquantitation of amyloid-β (amino terminal and carboxy terminal) peptides (Pg. 262, Column 2, Lines 3-6 and 49-50) wherein a source of aggregated, soluble β-amyloid is obtained from a homogenized brain tissue sample (Pg. 264, Fig.3) by dissolution with the solubilizing agent RIPA (Pg. 264, Column 2, Lines 29-31 and Pg. 265, Column 1, Lines 1-5), an anti-β-amyloid antibody is added, prior to analysis the β-amlyoid sample is desalted (Pg. 264, Column 1, Lines 10-11 and Column 2, Lines 1-3) and the precipitated antibody-β-amyloid complex is analyzed using Matrix-Assisted Laser Desorption Ionization/Time-Of-Flight-Mass Spectroscopy (MALDI-TOF) (Pg. 263, Fig. 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the method of β-amyloid quantitation taught by Clarke and the use of radiolabeled β-amyloid taught by Reik with the method of Kametani, because Isotope Dilution was well known at the time of invention as an accurate and definitive method for the measurement of endogenous and exogenous proteins in human samples and is capable of being used without the use of unstable radioactive tracers as well enabling the measurement of a internal standard simultaneously with the element of interest. The ordinary artisan would have been motivated to combine the two methods because Kametani states that MALDI-TOF is easier to perform and more sensitive than the Separation Exclusion-Liquid Chromatography-Mass Spectroscopy method taught by Clarke and the adaptation of the method of Clarke to the examination of other human proteins would have been obvious to one of ordinary skill in the art at the time of invention since the use of a labeling isotope would serve the same purpose as the methionine oxidation moiety found in Clarke. The ordinary artisan would have had a reasonable expectation of success in combining the two methods because both techniques are drawn to the isolation and characterization of soluble human proteins using mass spectroscopy.

Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Clark *et al.* (2001) in view of Riek *et al.* (2001) and Kametani *et al.* (1999) as applied to claims 1, 2, 4, 7, 8, 9, 11, 13, 18, 19, 21 and 22 above, and further in view of Schutze *et al.* (1998).

The teachings of Clarke *et al.* (2001) and Kametani *et al.* (1999) were discussed *supra.*

Schutze *et al.* teaches the use of laser dissection microscopy to capture samples of any shape and size including cell clusters and single cells. (Pg. 737, Column 1, Lines 38-40 and Column 2, Lines 1-2).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the methods of Clarke *et al.* and Kametani *et al.* with the addition of the laser dissection microscopy technique taught by Schutze because the high degree of accuracy over conventional dissection methods would enable the artisan to excise more completely those minute areas of tissue containing β-amyloid to be examined with less contamination from surrounding tissue and maintain the integrity of the tissue section. The ordinary artisan would have been motivated to combine the teachings of Clarke, Kametani and Schutze in order to obtain the highest purity of isolated β-amyloid for use in the experimental procedure by accurately excising only the specific tissue of interest for examination.

The ordinary artisan would have had a reasonable expectation of success in combining this technique with those of Clarke *et al.* and Kametani *et al.* since the method was used to successfully specific cellular structures and organelles and would have been readily adaptable to the excision of β-amyloid plaques.

Claims 5, 6 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Clarke *et al.* (2001), in view of Kametani *et al.* (1999) as applied to claims 1, 2, 4, 7, 8, 9, 11, 13, 18, 19, 21 and 22 above, and further in view of Wang *et al.* (1996).

The teachings of Clarke *et al.* (2001) and Kametani *et al.* (1999) were discussed *supra.*

Wang *et al.* teaches that soluble β-amyloid is found in the cerebrospinal and other biological fluids (Pg. 31894, Column 2, Lines 23-25), the use of synthetically produced β-amyloid (Pg. 31895, Column 1, Lines 62-64 and Column 2, Lines 1-2).

It would have been obvious to one of ordinary skill in the art to use the teachings of Wang, that soluble β-amyloid is found in bodily fluids and the use of synthetic β-amyloid peptide in combination with the method of the quantitative analysis of β-amyloid as taught by Clarke and the semi-quantitative measurement of β-amyloid as taught by Kametani because this would enable the artisan access to purified and labeled β-amyloid for use as a experimental standard.

The ordinary artisan with skill in the art would have been motivated to combine the teachings of Wang with those of Clarke and Kametani in order to examine β-amyloid found not just in plaques but also in other aqueous bodily fluids with the ease of using a cheap reproducible isotopically labeled synthetically produced standard. The ordinary artisan would have had a reasonable expectation of success in combining this method with the methods taught by the references above because all of the methods are drawn to the characterization and analysis by mass spectroscopy of human bodily proteins such that the ordinary artisan would have recognized the applicability of combining the methods.

Conclusion

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one with ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence or evidence to the contrary.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul C. Martin whose telephone number is 571-272-3348. The examiner can normally be reached on M-F 8am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on 571-272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Paul Martin
Examiner
Art Unit 1655

04/13/06

Primary Examiner